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An analysis by Dr. Jonathan Kimmelman, in the British Medical Journal provides an illuminating, clearly articulated discussion about the ethical dilemmas that challenge gene transfer experiments – essentially a kind of human genetic engineering involving somatic cells, in which a genetically engineered (foreign) gene is inserted into a vector (virus, bacteria, etc.), which is then injected into a human patient. Kimmelman notes the tenuous state of knowledge in the field, the anticipated risks– and most importantly the uncertainties about triggering unanticipated adverse consequences that will only emerge decades later.

Of course, all human experiments have unanticipated risks, some of the deadliest risks emerge only decades later. For example, after years of denial, the government finally acknowledged that a government approved experiment conducted between 1963 and 1985, in which 7,706 children who did not suffer from a life-threatening condition, were injected with growth hormone derived from the pituitaries of cadavers. The repercussions that resulted were deadly.

A new analysis by a team led by James L. Mills, M.D., chief of the Pediatric Epidemiology Section of the National Institute of Child Health and Human Development (NICHD) in the Journal of Pediatrics, April, 2004, examined the fate of 6,107 children / teenagers (of 7,706) who had received growth hormone injections from the National Hormone and Pituitary Program.

So far, 32 children are known to have developed Creutzfeldt-Jactob Disease (CJD, Mad Cow) decades later–while 1,419 required therapy to replace their adrenal hormones. So far, 32 children died of CJD and 59 died from adrenal crisis as a result of the experiment. The authors acknowledge 4 new CJD cases stating that CJD may take 30 years to develop, therefore more deaths from CJD may occur in this group in the future. They also acknowledge the uncertain outcome of the 1,599 who could not be traced. See: http://www.medicalnewsservice.com/fullstory.cfm?storyID=2226&fback=yes

Information for people treated with growth hormone from the NHPP is available at: http://www.niddk.nih.gov/health/endo/pubs/creutz/updatecomp.htm#5

Recent revelations about previously undisclosed fatalities in clinical trials demonstrate the need to re-examine current safeguards and ethical standards in in research involving human subjects. The current system, when examined independently, requires far greater oversight to protect against overreaching investigators who may have substantial financial stakes in a project. As we have witnessed, time and time again, when there is a conflict of interest, the safety of patient-subjects is always sacrificed in the interest of the sponsor's marketing goals.

Kimmelman article is available free at: http://bmj.bmjjournals.com/cgi/content/full/330/7482/79 Excerpt below.

An additional analysis of gene transfer research ethics in humans by Strachan and Read from their textbook: Human Molecular Genetics. (Excerpt below)

The focus is on experiments involving the alteration of germ line cells (sex cells), in which case the foreign genetic alteration is passed down in future generations. Dr. Dianne Irving has noted that the same exact technique used in somatic cell transfer can also be performed using germ line cells.These experiments raise additional ethical concerns because of their eugenic implications – i.e., artificial selection of genetic traits deemed desirable–who decides? Another problem may arise if those born with altered genetic compositions suffer unintended, terrible consequences resulting from these experimental explorations – who's responsible?

Both types of human experimentation have been discussed in bioethics for decades, and are among those proposed in California's Proposition 71.

We believe the evidence shows that the current research protection system under institutional review board oversight fails to perform its intended function. IRBs have veered away from safety issues engaging in lofty obfuscation to ensure easy enrollment of human subjects who are kept in the dark about the actual and foreseeable risks. IRBs and ethics boards engage in linguistic hyperbole to find a rationale for justifying their approval of illegitimate experiments – particularly where children are the

subjects. For their part, regulators – the FDA and The Office of Human Research Protections – have been shown to turn a blind eye and deaf ear to corner cutting of ethical standards and safety hazards. What is obviously lacking is a mechanism by which the research decision makers can be held accountable.

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Recent developments in gene transfer: risk and ethics

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Excerpt:

Fig 2 In a gene transfer, therapeutic DNA is combined with a vector (often of viral origin). Vectors can be injected into recipient's tissue directly or used to modify cells ex vivo for transplantation to the recipient

Several hazards associated with gene transfer have been verified by clinical experience and others are predicted on theoretical grounds. It therefore may be worth considering whether risks shown in studies of human gene transfer present any unusual ethical and social challenges and, if so, what should be done to tackle them. In this article I review several matters relating to human gene transfer – safety features that distinguish traditional drugs from agents used to transfer genes, ethical issues raised by uncertainties about risk and toxicological properties, and studies on safety.

The risk associated with human gene transfer has five conceptual characteristics that, although not unique, arise more often with this type of therapy (see box).

Firstly, active agents rather than chemicals are used to transfer genetic material. These vectors (usually retroviruses or adenoviruses) are therefore potentially capable of propagating themselves, recombining with other viruses, or carrying out complex programmes. [6]

Secondly, gene transfer functions on the basis of genetic information rather than on chemical structure. Thus, whereas chemical structures indirectly affect genetic functions, gene transfer directly participates in gene expression. Although this partly accounts for its therapeutic potential, it also underscores the possible potency of risks.

Thirdly, many agents act simultaneously as delivery devices through their vector as well as pharmacological agents through their transgene. Not only does this complicate the assessment of risk but each component can cooperate to worsen risks. For instance, the leukaemia that occurred in the X linked severe combined immunodeficiency trial may be attributable to the combined toxicity of the vector (which integrated near an oncogene) and the transgene (which may have helped transform T cells). [7]

Fourthly, gene transfer agents that stably modify a person's tissues can involve risks with long latencies. Continuous, life long exposure to transgenes or vectors increases the probability of subtle toxic properties becoming manifest over the long term.

Finally, much of the toxicity related to gene transfer is mediated through the immune system. Immune over reaction resulted in the death of a participant in a trial of an adenovirus vector in 1999. [8] Induced immunity against standard treatments (for example, factor IX protein in participants in the haemophilia B trial) or autoimmunity are also concerns with human gene transfer.

ETHICS OF RISK IN CLINICAL TRIALS

Does the character of risk with gene transfer generate new or major ethical challenges? This question may be best approached in three parts: what issues arise from immaturity of knowledge about risk, what ethical questions derive from toxicological characteristics, and what issues are raised by research aimed at improving the knowledge of risk?

Uncertainty and risk

While the toxicological properties of gene transfer agents remain obscure, ethics committees face formidable challenges in prosecuting two mandates for clinical trials [10]: evaluating the proportionality of risk and possible benefit, and overseeing risk disclosure during consent. The novelty of risks related to gene transfer means that uncertainties are more radical than those for conventional therapeutics, where a century of pharmacology provides a modicum of predictability.

The complexity of risk from gene transfer militates against the practice of using only local ethics committees to review trials (for example, in Canada or in some privately funded US trials, but not in the United Kingdom). [11] Ethics committees that encounter such protocols in jurisdictions that do not mandate central review should consider requiring the protocol's submission to a review body such as the Recombinant DNA Advisory Committee. In disclosing risk, investigators should go beyond simply mentioning the possibility of unforeseen consequences. Enough adverse events have occurred that investigators should state outright that previous human gene transfer trials involved unforeseen consequences.

A second set of ethical issues concerns how ethics committees assure the value of trials. All major ethics codes require that clinical research be capable of generating valuable medical knowledge.[10] In the past, gene transfer trials have often failed to do so. [12] Ethics committees and investigators should be attentive to the scientific quality of proposed trials. Firstly, gene transfer exposes participants to the possibility of serious, unforeseeable, and latent harms. Because trials, especially those in the early phases (accounting for most trials), are aimed at generalisable knowledge rather than therapy, such risks can only be justified if the trial can make major contributions to the advancement of scientific and medical knowledge. Demanding that trials maximise their gathering of information on toxicology improves a protocol's balance of risk and social value. Secondly, ethics committees should bear in mind that, after 15 years, no gene therapy has been commercialised. Owing to the uncertainties surrounding gene transfer, most trials should be conceptualised less as testing an agent's prospect of commercialisation and more as producing information that can be applied to the development of gene transfer. This is especially true because data on toxicity in humans are scarce and can only be gathered through trials. Ethics committees and investigators can fortify the value of gene transfer studies by considering plans for long term follow up and disseminating toxicological findings.

Important features of risk associated with gene transfer

Conceptual features

Uses active agents rather than chemicals
Composed of genetic material that directly affects gene expression
Functions simultaneously as delivery devices (vectors) and pharmacological agents (transgenes)
Stable genetic modification has risks with long latencies
Certain viral vectors present risks to public health and occupational risks

Methodological features

Limited number of animal models for predicting vector safety
Wide variability in humans' response to some vectors
Possible non-linear dose-response curves with gene transfer vectors

Considerations for investigators and ethics committees

Risk review – expertise of local ethics committees is generally insufficient to the task of ethics and risk review

Risk disclosure – that unexpected adverse events have occurred in previous trials should be disclosed, regardless of vector

Informed consent – severely ill participants tend to misconstrue trials as "therapy" rather than scientific experiments; consent procedures should aim to correct such misconceptions

Study design – trials should maximise their social utility by gathering and disseminating information, including results of long term follow up and autopsy

Eligibility criteria – the possibility of latent adverse events should be considered when selecting eligibility criteria for trials involving stable genetic modification

Tom Strachan and Andrew P. Read, Human Molecular Genetics (New York: Wiley-Liss, 1999), pp. 539-541:

Excerpt:

Section 22.6: The ethics of human gene therapy

All current gene therapy trials involve treatment for somatic tissues (somatic gene therapy). Somatic gene therapy, in principle, has not raised many ethical concerns. Clearly, every effort must be made to ensure the safety of the patients, especially since the technologies being used for somatic gene therapy are still at an undeveloped stage. However, confining the treatment to somatic cells means that the consequences of the treatment are restricted to the individual patient who has consented to this procedure. Many, therefore, view the ethics of somatic gene therapy to be at least as acceptable as, say, organ transplantation, and feel that ethical approval is appropriate for carefully assessed proposals. Patients who are selected for such treatments have severely debilitating, and often life-threatening, disease for which no effective conventional therapy is available. As a result, despite the obvious imperfections of the technology, it may even be considered to be unethical to refuse such treatment. The same technology has the potential, of course, to alter phenotypic characters that are not associated with disease, such as height for

instance. Such genetic enhancement, although not currently considered, can be expected to pose greater ethical problems; attempts to produce genetically enhanced animals have not been a success and in some cases have been spectacular failures (Gordon, 1999).

… Germline gene therapy, involving the genetic modification of germline cells (e.g. in the early zygote), is considered to be entirely different [from somatic gene therapy]. It has been successfully practiced on animals (e.g., to correct beta-thalassemia in mice). However, thus far, it has not been sanctioned for the treatment of human disorders, and approval is unlikely to be given in the near future, if ever.

Section 22.6.1: Human germline gene therapy has not been practiced because of ethical concerns and limitations of the technology for germline manipulation

The lack of enthusiasm for the practice of germline gene therapy can be ascribed to three major reasons:

[1] The imperfect technology for genetic modification of the germline

Germline gene therapy requires modification of the genetic material of chromosomes, but vector systems for accomplishing this do not allow accurate control over the integration site or event. In somatic gene therapy, the only major concern about lack of control over the fate of the transferred genes is the prospect that one or more cells undergoes neoplastic transformation. However, in germline gene therapy, genetic modification has implications not just for a single cell: accidental insertion of an introduced gene or DNA fragment could result in a novel inherited pathogenic mutation.

[2] The questionable ethics of germline modification

Genetic modification of human germline cells may have consequences not just for the individual whose cells were originally altered, but also for all individuals who inherit the genetic modification in subsequent generations. Germline gene therapy would inevitably mean denial of the rights of these individuals to any choice about whether their genetic constitution should have been modified in the first place (Wivel and Walters, 1993). Some ethicists, however, have considered that the technology of germline modification will inevitably improve in the future to an acceptably high level and, provided there are adequate regulations and safeguards, there should then be no ethical objections (see, for example, Zimmerman, 1991). At a recent scientific research meeting in the USA some scientists have also come out in support of such a development (Wadman, 1998).

From the ethical point of view, an important consideration is to what extent technologies developed in an attempt to engineer the human germline could subsequently be used not to treat disease but in genetic enhancement. There are powerful arguments as to why germline gene therapy is pointless. There are serious concerns, therefore, that a hidden motive for germline gene therapy is to enable research to be done on germline manipulation with the ultimate aim of germline-based genetic enhancement. The latter could result in positive eugenics programs, whereby planned genetic modification of the germline could involve artificial selection for genes that are thought to confer advantageous traits.

The implications of human genetic enhancement are enormous. Future technological developments may make it possible to make very large alterations to the human germline by, for example, adding many novel genes using human artificial chromosomes (Grimes and Cooke, 1998). Some people consider that this could advance human evolution, possibly paving the way for a new species, homo sapientissimus. To have any impact on evolution, however, genetic enhancement would need to be operated on an unfeasibly large scale (Gordon, 1999).

Even if positive eugenics programs were judged to be acceptable in principle and genetic enhancement were to be practiced on a small scale, there are extremely serious ethical concerns. Who decides what traits are advantageous? Who decides how such programs will be carried out? Will the people selected to have their germlines altered be chosen on their ability to pay? How can we ensure that it will not lead to discrimination against individuals? Previous negative eugenics programs serve as a cautionary reminder. In the recent past, for example, there have been horrifying eugenics programs in Nazi Germany, and also in many states of the USA where compulsory sterilization of individuals adjudged to be feeble-minded was practiced well into the present century.

[3] The questionable need for germline gene therapy

Germline genetic modification may be considered as a possible way of avoiding what would otherwise be the certain inheritance of a known harmful mutation. However, how often does this situation arise and how easy would it be to intervene? A 100% chance of inheriting a harmful mutation could most likely occur in two ways. One is when an affected woman is homoplasmic for a harmful mutation in the mitochondrial genome and wished to have a child. The trouble here is that, because of the multiple mitochondrial DNA molecules involved, gene therapy for such disorders is difficult to devise.

A second situation concerns inheritance of mutations in the nuclear genome. To have a 100% risk of inheriting a harmful mutation would require mating between a man and a woman both of whom have the same recessively inherited disease, an extremely rare occurrence. Instead, the vast majority of mutations in the nuclear genome are inherited with at most a 50% risk (for dominantly inherited disorders) or a 25% risk (for recessively inherited disorders). In vitro fertilization provides the most accessible way of modifying the germline. However, if the chance that any one zygote is normal is as high as 50 or 75%, gene

transfer into an unscreened fertilized egg which may well be normal would be unacceptable: the procedure would inevitably carry some risk, even if the safety of the techniques for germline gene transfer improves markedly in the future. Thus, screening using sensitive PCR-based techniques would be required to identify a fertilized egg with the harmful mutation. Inevitably, the same procedure can be used to identify fertilized eggs that lack the harmful mutation.